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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,915	05/10/2005	Gerd Haberhausen	21719-US	9560
22829	7590	04/14/2009		
Roche Molecular Systems, Inc. Patent Law Department 4300 Hacienda Drive Pleasanton, CA 94588			EXAMINER MUMMERT, STEPHANIE KANE	
			ART UNIT 1637	PAPER NUMBER
			MAIL DATE 04/14/2009	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,915	HABERHAUSEN ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 18 December 2008.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-3 and 5-7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-3 and 5-7 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date <u>12/18/08</u> .	6) <input type="checkbox"/> Other: _____

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DETAILED ACTION

Applicant's amendment filed on December 18, 2008 is acknowledged and has been entered. Claim 1 has been amended. Claims 4 and 8-9 have been canceled. Claims 1-3 and 5-7 are pending.

Claims 1-3 and 5-7 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL.

Previous Grounds of Rejection

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

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ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 6 of copending Application No. 10/534955 ('955 application) in view of Jannes et al. (WO96/00298; January 1996).

While these claims are not identical, they are not patentably distinct from one another. The claims of the copending '955 application are directed to a method for identification of a Gram positive pathogenic organism comprising amplification of a clinical sample, detecting amplification through hybridization, monitoring hybridization and identifying the organism(s). The claims of the instant application as amended are directed to a more narrow method of amplification and detection of pathogenic organisms comprising detection of a specific rRNA spacer region. In the copending application, claim 6 recites the detection of an rRNA spacer region. While the copending application does not specify the specific rRNA spacer sequence as comprising either 16S/23S or 18S/26S rRNA sequences, Jannes teaches specific detection of 16S/23S rRNA sequences. Considering the teaching by Jannes, "the spacer region situated between the 16S rRNA and the 23S rRNA gene, also referred to as the internal transcribed spacer (ITS), is an advantageous target region for probe development for detection of pathogens of bacterial origin" (p. 1-2), therefore it would have been prima facie obvious that 16S/23S or 18S/26S rRNA sequences fall within the scope of the rRNA sequences claimed in the copending application.

Furthermore, in the instant application, gram positive bacteria are detected, however this limitation is recited as a dependent claim and as part of a method that comprises identification of both gram negative and gram positive bacteria. The similarities between these two copending applications, including the steps of monitoring temperature dependence of hybridization and using this hybridization detection to identify specific organisms, render the method of the instant application obvious.

This is a provisional obviousness-type double patenting rejection.

3. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/532319 ('319 application). While these claims are not identical, they are not patentably distinct from one another. The claims of the copending '319 application are directed to a method for detecting the presence of bacterial pathogens in clinical samples, comprising steps directed to the isolation of nucleic acids, amplification and quantifying the amount of nucleic acids comprising a sequence that is specific for a bacterial pathogen, wherein the method of quantification comprises amplification, monitoring of amplification through a hybridization probe and through monitoring temperature dependence of hybridization. The claims of the instant application are directed to a similar method directed to the amplification and detection of bacterial pathogens. The differences between the current application and the '319 application lie in the specific recitation of analysis of specific aliquots of clinical specimens and comprising the use of multiple hybridization reagents in the instant application as contrasted with the real-time monitoring of amplification in the copending application, which falls within the scope of the amplification,

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detection and monitoring of temperature dependence of hybridization in the instant application.

While the copending '319 application does not recite 16S/23S or 18S/26S rRNA spacer sequence, this preselected sequence of the instant application falls within the scope of the claim as recited in the copending application. Furthermore, while the copending application does not specify the specific rRNA spacer sequence as comprising either 16S/23S or 18S/26S rRNA sequences, Jannes teaches specific detection of 16S/23S rRNA sequences. Considering the teaching by Jannes, "the spacer region situated between the 16S rRNA and the 23S rRNA gene, also referred to as the internal transcribed spacer (ITS), is an advantageous target region for probe development for detection of pathogens of bacterial origin" (p. 1-2), therefore it would have been prima facie obvious that 16S/23S or 18S/26S rRNA sequences fall within the scope of the rRNA sequences claimed in the copending application.

This is a provisional obviousness-type double patenting rejection.

New Grounds of Rejection as necessitated by IDS.

Claim Interpretation

The specification does not define the term "internal control" or "internal control template." Instead, the specification merely states, "it has been proven to be particular advantageous, if an internal control template is added. Usually, said control template comprises a selected sequence with primer binding sites complementary to at least one set of amplification primers used for amplification of the target nucleic sequences" (p. 20, line 30 to p. 21, line 4). Therefore, while Applicant argues that the internal control template comprises shared primer

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binding sites, neither the claims nor the specification require this limitation of the claims, only that this is usually the case. In the absence of such limitations, the term will be given a broadest reasonable interpretation, as reading on both control templates that are co-amplified using different primers for amplification of the target and control templates, and on control templates that are co-amplified using shared primer sites in the target and control templates.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on December 18, 2008 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al. (J. Clin. Micro., 2001, vol. 39, no. 9, p. 3047-3051, IDS reference) in view of Forsman et al. (Microbiology, 1997, vol. 143, p. 3491-3500) and Bergeron et al. (NEJM, 2000, vol. 343, no. 3, p. 175-179). Edwards teaches detection of Staphylococci using plural hybridization probes through monitoring of hybridization (Abstract).

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With regard to claim 1, Edwards teaches a method for identification of a pathogenic organism from a predetermined group of pathogens, comprising:

a) at least partially purifying nucleic acid from a clinical sample (p. 3048, col. 1, where DNA was extracted from type strains and clinical isolates),

b) subjecting at least a first aliquot of said clinical specimen to at least a first amplification and detection reaction in one reaction vessel (p. 3048, 'Light Cycler assays' heading, where the amplification and detection are carried out in the same vessel) comprising:

ba) at least a first set of amplification primers capable of amplifying a pre-selected nucleic acid sequence comprising the 16S rRNA region from several or all members of said predetermined group of pathogens (p. 3048, Table 2, where primers for amplification of the samples are

provided), wherein said predetermined group of pathogens comprises members of two or more genera (p. 3048, Table 1, where a variety of pathogens from two or more genera are detected),

bc) a plurality of hybridization reagents, said reagents together being capable of specifically detecting a pre-selected nucleic acid sequence comprising the 16S rRNA region from all members of said predetermined group of pathogens (p. 3048, Table 2, where the probes are designed to detect the pathogens), said detection step comprising:

bca) monitoring hybridization of each of said hybridization reagents at a pre-selected temperature, said hybridization being indicative for at least the genus of said pathogen present in the sample (Figure 1, where the hybridization of the probes at preselected temperatures is observed and monitored for each of the probes);

bc b) monitoring temperature dependence of hybridization, said temperature dependence being indicative of at least the species of said pathogenic organism (Figure 1, where the hybridization

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of the probes at preselected temperatures is observed and monitored for each of the probes; p. 3049, col. 1, where the indication of species for each melting temperature is provided; see Table 3 and 4);

and wherein said amplification and detection reaction is indicative of the identity of said pathogenic organism from a predetermined group of pathogens (Figure 1, where the hybridization of the probes at preselected temperatures is observed and monitored for each of the probes; p. 3049, col. 1, where the indication of species for each melting temperature is provided; see Table 3 and 4).

With regard to claim 2, Edwards teaches an embodiment of claim 1, further comprising subjecting at least a second aliquot of said clinical specimen to at least a second amplification and detection reaction in a different reaction vessel from said first aliquot of said clinical specimen being subjected to said first amplification and detection reaction in two different reaction vessels (p. 3048, col. 1, where multiple clinical samples were analyzed and where each individual specimen would be analyzed by amplification and detection in a separate aliquot and a separate reaction vessel).

With regard to claim 3, Edwards teaches an embodiment of claim 2, further comprising subjecting at least a third aliquot of said clinical specimen to at least a third amplification and detection reaction in a different reaction vessel from said first aliquot of said clinical specimen being subjected to said first amplification and detection reaction, and said second aliquot of said clinical specimen being subjected to said second amplification and detection reaction (p. 3048, where multiple clinical samples were analyzed and where each individual specimen would be analyzed by amplification and detection in a separate aliquot and a separate reaction vessel).

With regard to claim 7, Edwards teaches an embodiment of claim 2, wherein said first amplification and detection reaction and said second amplification and detection reaction are performed with the same thermocycling profile (p. 3048, col. 1, where the amplification reaction conditions applied to each of the clinical samples are the same, even if they are amplified and detected in the same or separate reaction vessels).

Regarding claim 1, Edwards does not teach that the primers target the spacer region between 16S and 23S rRNA. Forsman teaches sequencing and amplifying the 16S-23S rRNA spacer region for specific detection of Streptococcus and Staphylococcus species (Abstract).

With regard to claim 1, Forsman teaches amplifying a preselected nucleic acid sequence comprising the 16S/23S rRNA spacer region from several or all members of said predetermined group of pathogens (Abstract; p. 3492, col. 1, where the spacer region was amplified for sequencing; p. 3492, col. 1, where specific primers for each species were designed within the 16S/23S rRNA spacer region; p. 3494, Figure 1, Table 4).

Further regarding claim 1, Edwards does not explicitly teach the inclusion of an internal control template. Bergeron teaches the design of an internal control template for use in a LightCycler reaction (Abstract, p. 176).

With regard to claim 1, Bergeron teaches an embodiment comprising at least one internal control template, further comprising a hybridization reagent capable of specifically detecting said internal control template (p. 176, col. 1, 'primers and probes' heading, where genomic DNA and an internal control template were included in the amplification reaction and where pairs of hybridization probes for detection of the target and internal control were provided).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Edwards to target the 16S rRNA spacer sequence as taught by Forsman to arrive at the claimed invention with a reasonable expectation for success. As taught by Forsman, “the 16S-23S rRNA intergenic spacer of the ribosomal RNA operon (rrN) has proven useful for identification of strains and species”. Forsman also notes “the high evolutionary rate makes it possible to distinguish closely related bacterial species” (p. 3492, col. 1). (Abstract). Finally, Forsman teaches “the variation between the 16S-23S spacer sequences of different mastitis pathogens made it possible to design specific primer pairs for each of the nine species considered in this study” and “primer pairs were selected so that the same PCR cycling conditions could be employed for all of them” (p. 3494, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Edwards to target the 16S rRNA spacer sequence as taught by Forsman to achieve detection of a variety of species from within multiple genera using PCR amplification of the 16S-23S rRNA spacer region.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the methods taught by Edwards and Forsman to incorporate the internal control template as taught by Bergeron to arrive at the claimed invention with a reasonable expectation for success. As taught by Bergeron, “two pairs of fluorescently labeled adjacent hybridization probes, STB-F and STB-C and IC-F and IC-C, were also used for the rapid PCR assay to detect amplicons specific for group B streptococci and internal control amplicons, respectively” (p. 176, col. 1). Furthermore, Bergeron teaches, “methods were specific and sensitive enough to detect a single genomic copy of group B

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streptococcus. The internal control was always amplified when *S. agalactiae* DNA was absent, thereby showing that negative PCR results for group B streptococci were not attributable to the presence of inhibitors in the clinical samples" (p. 176, col. 2). Additionally, Edwards and Bergeron share the same format for detection of the amplified samples, using analysis of hybridization of labeled probes and melt curve analysis. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the method taught by Edwards and Forsman to incorporate the internal control template as taught by Bergeron to arrive at the claimed invention with a reasonable expectation for success.

5. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al. (J. Clin. Micro., 2001, vol. 39, no. 9, p. 3047-3051, IDS reference) in view of Forsman et al. (Microbiology, 1997, vol. 143, p. 3491-3500) and Bergeron et al. (NEJM, 2000, vol. 343, no. 3, p. 175-179) as applied to claims 1-3 and 7 above, and further in view of Jannes et al. (WO96/00298; January 1996, IDS reference).

Edwards in view of Forsman and Bergeron teaches all of the limitations of claims 1-3 and 7 as recited in the 103 rejection stated above. However, neither Edwards, Forsman or Bergeron teaches detection of gram positive and negative bacteria.

With regard to claim 5, Jannes teaches an embodiment of claim 2, wherein gram positive pathogenic organisms are exclusively identified by said first amplification and detection reaction, and gram negative pathogenic organisms are exclusively identified by said second amplification and detection reaction (Example 3, p. 78, where *Listeria*, a gram positive organism is detected; Example 4, p. 84-86, where *C. trachomatis*, a gram negative organism is detected).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Edwards, Forsman and Bergeron to include the targets of gram positive and gram negative bacteria as taught by Jannes to arrive at the claimed invention with a reasonable expectation for success. As taught by Jannes, "the present invention relates to nucleic acid probes derived from the spacer region between 16S and 23S ribosomal ribonucleic acid (rRNA) genes, to be used for the specific detection of eubacterial organisms in a biological sample by a hybridization procedure" (p. 1, lines 3-5). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Edwards, Forsman and Bergeron to include the targets of gram positive and gram negative bacteria as taught by Jannes to arrive at the claimed invention with a reasonable expectation for success.

6. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al. (J. Clin. Micro., 2001, vol. 39, no. 9, p. 3047-3051, IDS reference) in view of Forsman et al. (Microbiology, 1997, vol. 143, p. 3491-3500) and Bergeron et al. (NEJM, 2000, vol. 343, no. 3, p. 175-179) as applied to claims 1-3 and 7 above and further in view of Loeffler et al. (Diagnostic Microbiology and Infectious Disease, 2000, vol. 38, p. 207-212).

Loeffler teaches a method of amplification and detection of pathogenic organisms through the detection of the 18S rRNA gene (Abstract).

With regard to claim 6, Loeffler teaches an embodiment of claim 3, wherein fungal pathogens are exclusively identified in said third amplification and detection reaction (Abstract, Table 1, where all of the pathogens identified are fungal pathogens).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the general teachings of Edwards, Forsman and Bergeron to detect additional species, including yeast, as taught by Loeffler to arrive at the claimed invention with a reasonable expectation for success. While Edwards, Forsman and Bergeron are directed to the detection of bacterial species, one of ordinary skill would have recognized that the technique of species-specific detection using intergenic spacer regions as taught by Edwards and Forsman would be applicable to additional bacterial species and to yeast. Loeffler teaches the detection of yeast through targeting of the 18S rRNA spacer. As taught by Loeffler, “invasive candidiasis has become a major cause of morbidity and mortality in immune compromised hosts. Here we describe a fast and reliable DNA extraction and PCR amplification method in combination with slot blot hybridization assay” (Abstract). Loeffler also notes “the 18S rRNA genes of 7 yeast species... were completely sequenced” and “primers described bind tightly to conserved primer binding sites” which “would allow rapid cycle sequence of additional ribosomal genes throughout the whole kingdom of fungi” (p. 207). Therefore, it would have been obvious to one of ordinary skill in the art to include additional steps for detection of other species present in clinical samples, such as yeast, as taught by Loeffler to arrive at the claimed invention with a predictable result.

Response to Arguments

Applicant's arguments with respect to claims 1-3 and 5-7 have been considered but are moot in view of the new ground(s) of rejection.

Citation of Relevant Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bialek et al. (Clinical and Diagnostic Laboratory Immunology, 2002, vol. 9, no. 2, p. 461-469) teaches detection of yeast in tissue samples by nested and real-time amplification (Abstract).

Conclusion

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Examiner, Art Unit 1637

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